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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**WO 2004/092740 A3**

(54) Title: METHODS FOR IDENTIFYING THERAPEUTIC TARGETS INVOLVED IN GLUCOSE AND LIPID METABOLISM

(57) Abstract: The identification and evaluation of mRNA and protein targets associated with RNA binding proteins or mRNP complexes is described. In particular, the invention provides methods for identifying RNA binding proteins associated with physiological pathways that participate in glucose and lipid metabolism and mRNAs that exhibit coordinated gene regulation across those pathways. Candidate targets are provided that are useful for the diagnosis or treatment of diseases related to diseases, such as disease related to aberrant glucose and lipid metabolism, such as, for example, obesity, diabetes, and hypoglycemia.

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 G01N33/68 G01N33/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 G01N C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHELPS W. B.: "Innovative Systems Biology" 'Online! 6 November 2002 (2002-11-06), XP002291620 Retrieved from the Internet: URL: <a href="http://www.ribonomics.com/news/presentations/ribonomics_RNA_in_Drug_Development.pdf">http://www.ribonomics.com/news/presentations/ribonomics_RNA_in_Drug_Development.pdf</a> > 'retrieved on 2004-08-05! the whole document	1-11, 14, 15, 18-20, 30, 37
Y	----- -/-	12

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TILLMAR LINDA ET AL: "Hypoxia may increase rat insulin mRNA levels by promoting binding of the polypyrimidine tract-binding protein (PTB) to the pyrimidine-rich insulin mRNA 3'-untranslated region." MOLECULAR MEDICINE (CAMBRIDGE, MASS.) MAY 2002, vol. 8, no. 5, May 2002 (2002-05), pages 263-272, XP002291619 ISSN: 1076-1551 the whole document	31-33
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X	CHEATHAM B. ET AL.: "A ribonomic analysis of adipocytes: a systems biology tool" 'Online! 2 December 2002 (2002-12-02), XP002291621 Retrieved from the Internet: URL: <a href="http://www.ribonomics.com/news/presentations/ribonomics_MetabolicDisease2002Poster.pdf">http://www.ribonomics.com/news/presentations/ribonomics_MetabolicDisease2002Poster.pdf</a> > 'retrieved on 2004-08-05! the whole document	1-11,14, 15, 18-20, 25-30,37
X	US 2002/004211 A1 (TENENBAUM SCOTT A ET AL) 10 January 2002 (2002-01-10)  paragraph '0004!; figures 2,4,8; table 1 paragraph '0019! paragraph '0049! paragraph '0064! paragraph '0072! - paragraph '0074!	1,6,7, 9-12,14, 20-29
X	CEMAN S ET AL: "Isolation of an FMRP-associated messenger ribonucleoprotein particle and identification of nucleolin and the fragile X-related proteins as components of the complex." MOLECULAR AND CELLULAR BIOLOGY. DEC 1999, vol. 19, no. 12, December 1999 (1999-12), pages 7925-7932, XP002302896 ISSN: 0270-7306 the whole document	21-24
		-/-

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>OHASHI SACHIYO ET AL: "Identification of mRNA/protein (mRNP) complexes containing Puralpha, mStaufen, fragile X protein, and myosin Va and their association with rough endoplasmic reticulum equipped with a kinesin motor."</p> <p>THE JOURNAL OF BIOLOGICAL CHEMISTRY. 4 OCT 2002, vol. 277, no. 40, 4 October 2002 (2002-10-04), pages 37804-37810, XP002302897 ISSN: 0021-9258 the whole document</p>	21-24
X	<p>TENENBAUM SCOTT A ET AL: "Ribonomics: Identifying mRNA subsets in mRNP complexes using antibodies to RNA-binding proteins and genomic arrays"</p> <p>METHODS (ORLANDO), vol. 26, no. 2, February 2002 (2002-02), pages 191-198, XP002291623 ISSN: 1046-2023 page 194, right-hand column, line 12 - page 195, left-hand column, paragraph 1</p>	21-24
X	<p>GAVIN A-C ET AL: "Functional organization of the yeast proteome by systematic analysis of protein complexes"</p> <p>NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 415, January 2002 (2002-01), pages 141-147, XP002958851 ISSN: 0028-0836 page 143, right-hand column, last paragraph - page 144, left-hand column, paragraph 1; figure 3</p>	21-24
X	<p>TILLMAR LINDA ET AL: "Control of insulin mRNA stability in rat pancreatic islets. Regulatory role of a 3'-untranslated region pyrimidine-rich sequence."</p> <p>THE JOURNAL OF BIOLOGICAL CHEMISTRY. 11 JAN 2002, vol. 277, no. 2, 11 January 2002 (2002-01-11), pages 1099-1106, XP002302898 ISSN: 0021-9258 the whole document</p>	31-33
Y	-/-	35,36

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HIERONYMUS HALEY ET AL: "Genome-wide analysis of RNA-protein interactions illustrates specificity of the mRNA export machinery." NATURE GENETICS. FEB 2003, vol. 33, no. 2, February 2003 (2003-02), pages 155-161, XP002302899 ISSN: 1061-4036 the whole document	34
Y		35, 36
X	LELIVELT M J ET AL: "Yeast Upf proteins required for RNA surveillance affect global expression of the yeast transcriptome" MOLECULAR AND CELLULAR BIOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, US, vol. 19, no. 10, October 1999 (1999-10), pages 6710-6719, XP002977598 ISSN: 0270-7306 the whole document	34
A	RIBONOMICS INC.: "Research & Technology" 'Online!' 17 March 2003 (2003-03-17), XP002291622 Retrieved from the Internet: URL: <a href="http://web.archive.org/web/20030317064208/http://www.ribbonomics.com/technology/index.html">http://web.archive.org/web/20030317064208/http://www.ribbonomics.com/technology/index.html</a> 'retrieved on 2004-08-05!	
A	TENENBAUM S A: "IDENTIFYING mRNA SUBSETS IN MESSENGER RIBONUCLEOPROTEIN COMPLEXES BY USING cDNA ARRAYS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 97, no. 26, 19 December 2000 (2000-12-19), pages 14085-14090, XP000995310 ISSN: 0027-8424	
A	KEENE JACK D: "Ribonucleoprotein infrastructure regulating the flow of genetic information between the genome and the proteome" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 98, no. 13, 19 June 2001 (2001-06-19), pages 7018-7024, XP002291624 ISSN: 0027-8424	
		-/-

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KEENE JACK D ET AL: "Eukaryotic mRNPs may represent posttranscriptional operons" MOLECULAR CELL, vol. 9, no. 6, June 2002 (2002-06), pages 1161-1167, XP002291625 ISSN: 1097-2765 ----- RODGERS NANCY D ET AL: "Identifying mRNAs bound by RNA-binding proteins using affinity purification and differential display." METHODS (SAN DIEGO, CALIF.) FEB 2002, vol. 26, no. 2, February 2002 (2002-02), pages 115-122, XP002291626 ISSN: 1046-2023 ----- BROWN V ET AL: "Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome." CELL. 16 NOV 2001, vol. 107, no. 4, 16 November 2001 (2001-11-16), pages 477-487, XP002291627 ISSN: 0092-8674 -----	
P,X	KNOCH KLAUS-PETER ET AL: "Polypyrimidine tract-binding protein promotes insulin secretory granule biogenesis." NATURE CELL BIOLOGY. MAR 2004, vol. 6, no. 3, March 2004 (2004-03), pages 207-214, XP002302900 ISSN: 1465-7392 the whole document ----- HEROLD ANDREA ET AL: "Genome-wide analysis of nuclear mRNA export pathways in Drosophila." THE EMBO JOURNAL. 15 MAY 2003, vol. 22, no. 10, 15 May 2003 (2003-05-15), pages 2472-2483, XP002302901 ISSN: 0261-4189 the whole document -----	31,33 34

**INTERNATIONAL SEARCH REPORT**

PCT/US2004/010686

**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20,25-30,37

screening methods involving the comparison of RNA or protein levels of at least one component of an isolated mRNP from two different cellular phenotypes or states (e.g. treated vs. untreated)

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2. claims: 21-24

method for identifying a gene or gene product involved in a physiological pathway by isolating additional components of an mRNP complex that contains a component already known to be involved in said pathway

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3. claims: 31,32

method for identifying an insulin production regulating protein agent characterized by its ability to bind to the 3' or 5' untranslated region of a preproinsulin mRNA

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4. claim: 33

mRNP complex involved in glucose or lipid metabolism which comprises PTB protein and an mRNA associated with PTB

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5. claims: 34-36

method for identifying a component of an mRNP complex by expression profiling of RNA with or without prior inhibition of expression of an RNA binding protein

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## Information on patent family members

PCT/US2004/010686

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 2002004211	A1	10-01-2002	US 2003235830 A1	25-12-2003
			US 2003211466 A1	13-11-2003
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